

# Suture fusion in normal and pathological development is constrained by the network architecture of the human skull

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**Abstract** - Birth defects such as cleft palate and craniosynostosis affect the correct development of the skull, producing morphological malformations not specifically controlled by genetic or epigenetic factors. Only a few of the 80 human skull sutures at birth are associated with these conditions. To assess the susceptibility of each craniofacial suture to be lost, we used a network model of the skull to quantify the link reliability (an index based on stochastic block modeling and Bayesian inference) of each articulation. Sutures that fuse during normal development and as part of these maladies show statistically significant lower reliability scores, which suggests that the network architecture of the skull predisposes these sutures as targets for fusion. Our findings indicate that skull bone arrangement might act as an epigenetic factor, predisposing some sutures to be lost both in normal and pathological development, also affecting the long-term evolution of the skull.

**Keywords:** Birth defects; Cleft palate; Craniosynostosis; Anatomical Network Analysis; Stochastic Block Models; Bayesian inference

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## INTRODUCTION

Craniofacial sutures are primary sites of bone growth and remodeling; adequate formation and maintenance of sutures is therefore important for a healthy development of the head and brain. Sutures fuse as part of the normal developmental process of the skull when taking place at the right time. However, deviations from the normal process of suture pattern formation in the human skull usually cause birth defects, such as cleft palate and craniosynostosis. The former is a condition in which the bones of the hard palate (maxilla and palatine) fail to form the midpalatal suture, with a prevalence of about 15 in 10,000 live births<sup>1</sup>; this condition is often associated with a cleft lip, causing health and social problems for the child<sup>1</sup>. The latter is a condition in which one or more sutures between cranial bones (frontal, parietal, temporal, and occipital) fuse prematurely, with a prevalence of about 5 in 10,000 live births<sup>2</sup>; when these premature fusions are not treated surgically, they can cause head malformations due to compensatory growth of other sutures<sup>3</sup>, sometimes provoking severe brain damage due to an increase of intracranial pressure<sup>4</sup>. Both conditions can occur in isolation<sup>1,5</sup>, or as part of a variety of congenital disorders, such as Van der Woude and X-linked intellectual disability syndromes<sup>1</sup>, or Apert and Crouzon syndromes<sup>6</sup>.

Genetic and epigenetic factors participate in the formation and maintenance of craniofacial sutures. The number of genes identified carrying mutations associated with these two pathologies has grown in the last two decades<sup>1,7</sup>. For example, more than 60 genes are now known to carry mutations associated with craniosynostosis<sup>7</sup>: some of them show specificity for a suture in the context of a syndrome (e.g., *ASXL1* and metopic suture in the Bohring-Opitz syndrome), others predispose to more than one type of craniosynostosis (e.g., *FGFR2* in coronal, sagittal, and multisuture synostoses), while most of them are not specifically associated with suture development, but to osteogenesis in general (e.g., *ALX4*, *EFNA4*, and *TGFBR2*). Epigenetic factors include, among many others, bio-mechanical stress, hypoxia, and use of drugs during pregnancy<sup>1,8,9</sup>. Epigenetic factors are even less specific than genetic ones; for example, maternal smoking has been associated to a predisposition for both cleft palate and some craniosynostoses<sup>10,11</sup>.

Only a small fraction of the more than 80 articulations that make up the human skull before birth are associated with these birth defects. However, we still do not know which factors predispose some sutures but no others to fuse pathologically or to not form at all. Here we address this question by modeling the skull as a network in which nodes and links formalize bones and their articulations (FIG. 1). We use the reliability formalism developed for network models<sup>12</sup> to infer

the susceptibility of craniofacial sutures to be lost in pathological conditions.

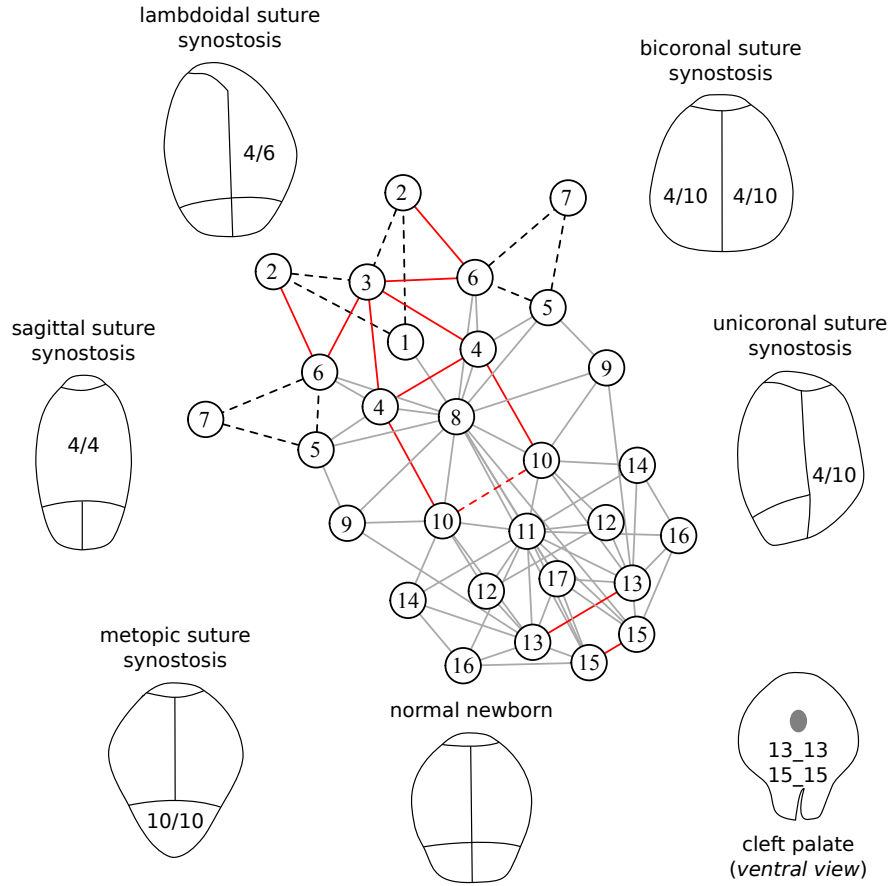


FIG. 1. The arrangement of bones in the human skull at birth modeled as a network; nodes and links represent bones and articulations (sutures and synchondroses). Red links indicate sutures associated with cleft palate and craniosynostosis conditions; dashed links are articulations lost during the normal development due to fusion. Note that the metopic suture between the left and right frontal bones fuses in pathological and normal development. Drawings illustrate the shape of the head in some of the conditions studied. *Labels: 1 basilar, 2 lateral occipital, 3 occipital plane, 4 parietal, 5 squama, 6 petromastoid, 7 tympanic ring, 8 sphenoidal, 9 zygomatic, 10 frontal, 11 ethmoidal, 12 nasal, 13 maxilla, 14 lacrimal, 15 palatine, 16 nasal concha, 17 vomer.*

Anatomical network models have been used before, for example, to identify developmental constraints in skull evolution<sup>13,14</sup>, analyze the evolution of tetrapod disparity in morphospace across phylogeny<sup>15</sup>, and model the growth of human skull bones<sup>16</sup>. A recent comparison of network models of craniosynostosis conditions showed that, despite the associated abnormal shape variation, skulls with different types of craniosynostosis share a same general pattern of network

modules<sup>17</sup>.

Here, we want to investigate whether the topological arrangement of bones and articulations predicts which sutures are more susceptible to be lost; in other words, we want to assess if the architecture of the skull acts as an agent that constraints the formation and fusion of sutures. A common feature of the topology of complex networks such as the skull is that one can identify groups of nodes (bones) that have well-defined patterns of connections (i.e., articulations) with other groups of nodes<sup>12</sup>. Such realization allows one to identify links that are topologically unexpected. If the architecture of the skull is driving the fusion of articulations, we surmise that there is a relationship between the susceptibility of an articulation to fuse and the topological 'unexpectedness' of such articulation. To quantify such susceptibility, we use the *link reliability* score, that is the probability that a connection exists in the network given the observed (newborn) topology of the skull<sup>12</sup>. A low score means that the presence of this articulation is rare, that is, not commonly expected in the given arrangement of bones (see *Methods* for details on how this is estimated). Importantly, the link reliability formalism has been used in other complex systems to accurately predicting missing and spurious interactions in social, neural, and molecular networks<sup>12</sup>, to predict harmful interactions between pairs of drugs<sup>18</sup> and to predict the apparition of conflicts in teams<sup>19</sup>.

## RESULTS

First we investigated the relationship between the link reliability score and the susceptibility of an articulation to fuse during normal development. To that end, we compared the reliability score of those articulations that fuse during the normal development of the skull to those that do not. We find that sutures that normally fuse have significantly lower reliability scores than those that do not (Mann-Whitney-Wilcoxon: one sided  $W=206.0$ ,  $p\text{-value} = 0.0055$ ;  $\text{Mean}(\text{fused}) = 0.3485$ ;  $95\% \text{ CI}(\text{non-fused}) = (0.4124, \text{inf})$ )(Fig. 2); which is in agreement with our hypothesis that during normal development there is a tendency to lose articulations that are topologically rare in the newborn skull. (Reliability scores are available in the *Supplementary Materials*. See *Methods* for details on the quantification of link reliability and statistical analysis.)

Next, we investigated whether sutures that fuse in pathological conditions are topologically different from sutures that do not form (including no-links, i.e., articulations that never appear among bones but that can be analyzed thanks to the network model of the skull). To that end, we compared the reliability score of sutures that occur in cleft palate and craniosynostosis conditions to that of

those sutures that do not form or do not fuse during the normal development of the skull (Fig. 2). We found that sutures associated with pathological conditions have significantly lower reliability scores than sutures that are not (one-sided,  $W = 116$ ,  $p\text{-value} = 1.022E^{-4}$ ;  $\text{Mean}(\text{pathological}) = 0.3244$ ; 95% CI (non-pathological and non-fused) = (0.4417, inf)); which shows that sutures associated to pathological conditions are also unexpected from a topological point of view.

Interestingly, we find no statistical difference between the reliability scores of sutures that are associated to pathological conditions and those that fuse during normal development (two-sided  $W = 44.5$ ,  $p\text{-value} = 0.196$ ; 95% CI (fused) = (0.3389, 0.3668)). This finding suggests that while skull architecture is an important factor in the loss of sutures during both pathological and normal development, there are non-topological factors that discriminate between normal and pathological loss of sutures.

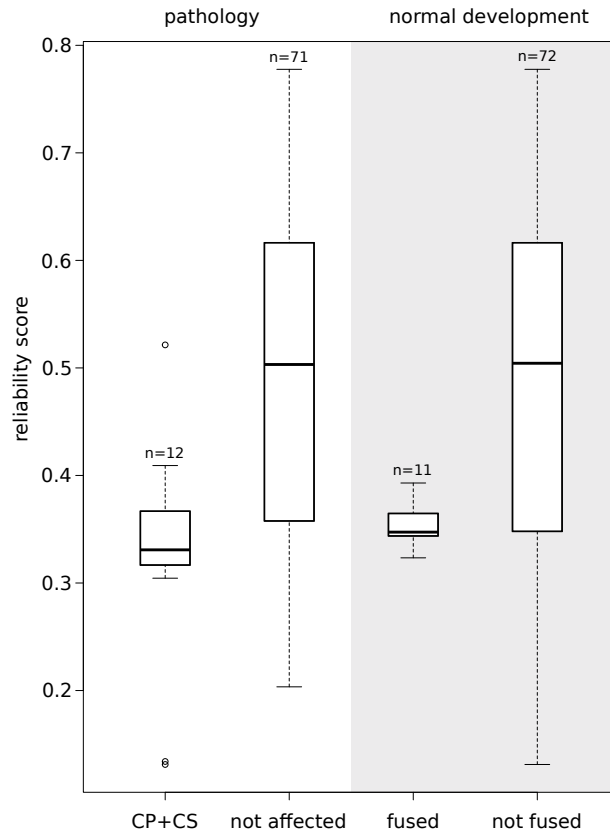


FIG. 2. Box plot comparing link reliability scores. Sutures associated with cleft palate and craniosynostosis (CP+CS) have lower reliability than those that are not associated (*left*, white panel). Sutures that fuse during normal development also have lower reliability than those that not do so (*right*, gray panel).

## DISCUSSION

Our results suggest that the whole architecture of craniofacial articulations of the skull might act itself as an epigenetic factor, making some sutures to be more susceptible to be lost than others. That some regions of the skull act epigenetically (e.g., via bio-mechanical signaling) to predispose sutures to a premature fusion was already proposed by Moss in the context of the functional matrix hypothesis<sup>20</sup>. Here we show that the most susceptible sutures to be prematurely fused (i.e., those with low reliability scores) are precisely the ones associated with cleft palate and craniosynostosis. Thus, we propose that the very arrangement of bones in the skull predisposes epigenetically some sutures as targets of pathological conditions. We are not yet in a position to offer a mechanistic explanation for the relationship reported here, which we believe may be related to the same developmental mechanism that regulate compensatory growth of bones after premature synostoses<sup>3,21,22</sup>. However, our results also suggest that such mechanisms should not be different between normal and pathological conditions, since sutures and synchondroses that are lost during normal development of the skull also show low reliability scores.

If, as our results suggest, the system of articulations of skull bones is able to self-regulate epigenetically the formation and maintenance of sutures and synchondroses, this might have consequences also at an evolutionary scale. In craniosynostosis conditions, the number of bones is reduced due to the early suture fusions, much in the same way as the net reduction in the number of bones during vertebrate evolution<sup>13,23,24</sup>; as a consequence, it has been postulated that craniosynostosis could be used as an informative model for skull evolution<sup>25</sup>. Our results suggest that this is not a mere analogy, but that similar epigenetic processes might act in regulating the configuration of bone arrangements in the skull both in development and in evolution.

Pathological conditions of the human skull, including cleft palate and craniosynostosis, are a medical and social problem that needs special attention from the research community. In addition, they represent medical examples of more general developmental and evolutionary processes found in all tetrapods. Both aspects, the medical and the biological, need and can be integrated in order to reach a better understanding that could lead to improve treatments as well as to further our knowledge about fundamental evolutionary questions.

## METHODS

### A network model of the skull

We built a network model of the human skull at birth based on anatomical descriptions<sup>26</sup> and information of ossification timing and fusion events<sup>27</sup>. The nodes and links of the network model formalize the bones and articulations (sutures and synchondroses) of the skull, respectively (FIG. 1).

### Estimation of link type probability using stochastic block models

Stochastic block models are good model to describe the patterns of connections in complex networks. In such models, nodes are assigned to groups and the probability of a link existing between two pairs of nodes is given by a matrix that specifies the connectivity rate between nodes belonging to pairs of blocks. For a given network, good stochastic block models are those that group nodes that have a similar pattern of connections; for instance, in our case we could group together nodes *vomer* and *palatine* since both tend to connect to similar nodes (*sphenoid*, *ethmoid*, *maxila*) along with a disconnection to similar nodes (*parietal*, *zygomatic*, *frontal*, etc.).

Within this description, links between pairs of nodes that belong to groups that are densely interconnected are more likely than those links between pairs of nodes belonging to groups that are sparsely connected. For instance, in the previous example a suture existing between *palatine* and *maxila* is much more likely than a suture between *palatine* and *parietal*. To mathematically formalize this intuition, we compute the reliability score, that is the probability that a link exists given the network of connections we observe (the newborn skull in our case) using stochastic block models as the basis for our inference algorithm. In practice, our algorithm samples the space of partitions of nodes into groups taking into account how good a given partition manages to classify nodes with similar patterns of connections into the same group. For each of this partitions, each link between a pair of nodes  $(i, j)$  has a specific probability. The reliability score of link  $N_{ij}$  is then a weighted average of the probabilities of that link for each sampled partition.

Mathematically, we formalize the previous arguments in a Bayesian framework as follows. Given a family of models  $\mathcal{M}$ , the probability that  $N_{ij} = 1$  given the observed network  $N^O$  (that is the matrix of connections) is<sup>12</sup>

$$p(N_{ij} = 1|N^O) = \int_{\mathcal{M}} dM p(N_{ij} = 1|M) p(M|N^O), \quad (1)$$

where the integral is over all the models  $M$  in ensemble  $\mathcal{M}$ . We can rewrite this equation using Bayes theorem and obtain<sup>12,28</sup>

$$p(N_{ij} = 1|N^O) = \frac{\int_{\mathcal{M}} dM p(N_{ij} = 1|M) p(N^O|M) p(M)}{\int_{\mathcal{M}} dM p(N^O|M) p(M)} . \quad (2)$$

Here,  $p(N^O|M)$  is the probability of the observed interactions given model  $M$  and  $p(M)$  is the *a priori* probability of a model, which we assume to be model-independent  $p(M) = \text{const.}$

In our approach, we assume that the family of stochastic block models is a good ensemble to describe the connectivity in a complex network (in our case that of the human skull). Therefore, each model  $M = (P, Q)$  is completely determined by a partition  $P$  of bones into groups and the group-to-group interaction probability matrix  $Q$ . For a given partition  $P$ , the matrix element  $Q(\alpha, \beta)$  is the probability of a suture joining a bone in group  $\alpha$  with a bone in group  $\beta$ . Thus, if  $i$  belongs to group  $\sigma_i$  and  $j$  to group  $\sigma_j$  we have that<sup>28</sup>

$$p(N_{ij} = 1|M) = Q(\sigma_i, \sigma_j) ; \quad (3)$$

and

$$p(N^O|M) = \prod_{\alpha \leq \beta} Q(\alpha, \beta)^{n^1(\alpha, \beta)} (1 - Q(\alpha, \beta)^{n^0(\alpha, \beta)}) , \quad (4)$$

where  $n^1(\alpha, \beta)$  is the number of sutures between bones in groups  $\alpha$  and  $\beta$  and  $n^0(\alpha, \beta)$  is the number of disconnections between bones in groups  $\alpha$  and  $\beta$ .

The integral over all models in  $\mathcal{M}$  can be separated into a sum over all possible partitions of the bones into groups, and an integral over all possible values of each  $Q(\alpha, \beta)$ . Using this together with Eqs. (2), (3) and (4), and under the assumption of no prior knowledge about the models ( $p(M) = \text{const.}$ ), we have

$$p(N_{ij} = 1|N^O) = \frac{1}{Z} \sum_P \int_0^1 dQ Q(\sigma_i, \sigma_j) \prod_{\alpha \leq \beta} Q(\alpha, \beta)^{n^1(\alpha, \beta)} (1 - Q(\alpha, \beta)^{n^0(\alpha, \beta)}) , \quad (5)$$

where the integral is over all  $Q(\alpha, \beta)$  and  $Z$  is the normalizing constant (or partition function). Using these expressions in Eq. (6), one obtains

$$p(N_{ij} = 1|N^O) = \frac{1}{Z} \sum_P \left( \frac{n^1(\sigma_i, \sigma_j) + 1}{n(\sigma_i, \sigma_j) + 2} \right) \exp(-H(P)) , \quad (6)$$

where the sum is over all partitions of bones into groups,  $n(\sigma_i, \sigma_j) = n^1(\sigma_i, \sigma_j) + n^0(\sigma_i, \sigma_j)$  is the total number of possible sutures between groups  $\sigma_i$  and  $\sigma_j$ , and  $H(P)$  is a function that depends



on the partition only

$$H(P) = \sum_{\alpha \leq \beta} \left[ \ln(n(\alpha, \beta) + 1) + \ln \left( \frac{n(\alpha, \beta)}{n^1(\alpha, \beta)} \right) \right], \quad (7)$$

This sum can be estimated using the Metropolis algorithm<sup>12,29</sup> as detailed next.

## Implementation details

The sum in Eq. (6) cannot be computed exactly because the number of possible partitions is combinatorially large, but can be estimated using the Metropolis algorithm<sup>12,29</sup>. This amounts to generating a sequence of partitions in the following way. From the current partition  $P^0$ , select a random bone and move it to a random new group giving a new partition  $P^1$ . If  $H(P^1) < H(P^0)$ , always accept the move; otherwise, accept the move only with probability  $P = e^{H(P^0) - H(P^1)}$ .

By doing this, one gets a sequence of partitions  $\{P^i\}$  such that one can approximate the integral in 6 as<sup>29</sup>

$$p(N_{ij} = 1 | N^O) \approx \frac{1}{S} \sum_{P \in \{P^i\}} \frac{n^1(\sigma_i, \sigma_j) + 1}{n(\sigma_i, \sigma_j) + 2}, \quad (8)$$

where  $S$  is the number of sampled partitions in  $\{P^i\}$ .

In practice, it is useful to “thin” the sample  $\{P^i\}$ , that is, to consider only a small fraction of evenly spaced partitions so as to avoid the computational cost of sampling very similar partitions which provide very little additional information. Moreover, one needs to make sure that sampling starts only when the sampler is “thermalized”, that is, when sampled partitions are drawn from the desired probability distribution (which in our case is given by  $e^{-H(P)}/Z$ ). Our implementation automatically determines a reasonable thinning of the sample, and only starts sampling when certain thermalization conditions are met. Therefore, the whole process is completely unsupervised. The source code of our implementation of the algorithm is publicly available from <http://http://seeslab.info/downloads/network-c-libraries-rgraph/> and <http://github.com/seeslab/rgraph>.

## Statistical analysis

We divided the links of the network model of the skull into three groups: (group 1) associated with cleft palate and craniosynostosis, (group 2) fused during a normal development, and (group 3)

not fused during normal development. Groups follow the literature reviews listed in the references and common knowledge. TABLE I shows the sutures most commonly associated with cleft palate and craniosynostosis, as well as those sutures that fuse in a normal development of the human skull.

We performed an independent one-sided Mann-Whitney U test for the following pairs of groups: groups (group 2 vs. group 3, group 1 vs. group 3, and group 1 vs. group 2). We tested the null hypothesis of equal distribution between groups against the alternative hypothesis that:

1. sutures in group 2 have lower reliability scores than sutures in groups 1+3;
2. sutures in group 1 have lower reliability than those in group 3;
3. sutures in group 2 have lower reliability scores than those in group 1.

We estimated the median of the difference between groups and a non-parametric 95% confidence interval. The statistical analysis was performed with function `wilcox.test` in R<sup>30</sup>.

TABLE I. Articulations modified during cleft palate, craniosynostosis, and normal development.

<b>Craniofacial joint</b>	<b>Between</b>	<b>Condition</b>
intermaxillary	left and right maxilla	cleft palate
interpalatal	left and right palatine	cleft palate
sagittal	left and right parietal	craniosynostosis
coronal	frontal and parietal	craniosynostosis
lambdoid	parietal and occipital plane	craniosynostosis
occipitomastoid	petromastoid and occipital plate	craniosynostosis
	petromastoid and lateral occipital	
metopic	left and right frontal	craniosynostosis
		normal development of the frontal bone
petrosquamosal	petromastoid and squamosal	normal development of the temporal bone
petrotympanic	petromastoid and tympanic ring	normal development of the temporal bone
squamotympanic	squamosal and tympanic ring	normal development of the temporal bone
basilateral	basilar and lateral occipital	normal development of the occipital bone
occipitolateral	lateral occipital and occipital plane	normal development of the occipital bone

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All authors designed the study. BE-A made the network model of the skull. RG, MS-P, and TV-C analyzed the network model and calculated reliability scores. All authors discussed the results and wrote the manuscript.

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